REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1 and 4-83 will be pending in the application. Claims 2 and 3 previously were canceled. Claims 1, 4-13, 23, 24, and 27-29 are rejected. Objections to claims 68 and 70 for depending from a rejected base daim also have been made. Claim 1 is amended herein, as supported by in the specification, for example, by Example 7. Claim 83 is added as supported in the specification, for example at pages 17-18. Applicants note with appreciation the indication of allowability of claims 72-82.

Claims 14-22, 25, 26, 30-67, 69, and 71 are withdrawn from consideration. Applicants regretfully note that claim 22 has been withdrawn from consideration as being drawn to a nonelected invention. Applicants respectfully assert that the withdrawal of claim 22 was in error, as claim 22 was rejoined with elected Groups I and VI (see Office Actions mailed August 15, 2002 and April 30, 2003). Rejoinder of that claim is respectfully requested.

No new matter has been introduced by way of this amendment.

Applicants note with appreciation the acceptance of the formal drawings submitted by the amendment filed July 30, 2003.

I. Amended claims 1 and 4-13 are patentable over the Hubbard reference.

Claims 1 and 4-13 are rejected under 35 U.S.C. § 102(b) for alleged anticipation, or, in the alternative, under 35 U.S.C. § 103 for alleged obviousness, over Hubbard*et al.* (*Mut. Res.*, 85/4:264 (1981)) ("Hubbard" or "the Hubbard reference"). Applicants have amended claim 1 to recite methods for making hypermutable plant or yeast cells. The Hubbard reference describes exposure of bacterial cells to dimethylanthracene in the presence of hepatocytes to approximate metabolic activation of the chemical *in vivo*. As the Hubbard reference neither teaches nor suggests a method for making a hypermutable plant or yeastcell *in vitro* by exposing the cell to an anthracene compound, claims 1 and 4-13 are patentable over that reference. Accordingly, withdrawal of the rejection is respectfully requested.

II. Claims 1 and 4-13 are patentable over the LaVoie reference in combination with any one of the Krahn, Wigley, or Slaga references and further in view of the Hubbard reference.

Claims 1 and 4-13 are rejected under 35 U.S.C. § 103 for alleged obviousness over LaVoie *et al.* (*Carcinogenesis*, 6:1483-1488 (1985)) ("LaVoie" or "the LaVoie reference") in view of any one of Krahn *et al.* (*Mut. Res.*, 46:27-44 (1997)) ("Krahn" or "the Krahn reference"), Wigley *et al.* (*Int. J. Cancer*, 23:691-696 (1979)) ("Wigley" or "the Wigley reference"), and Slaga *et al.* (*Cancer Res.*, 38:1699-1704 (1978)) ("Slaga" or "the Slaga reference"), further in view of the Hubbard reference. Applicants note that Machala *et al.* (*Mut. Res.*, 407:49-62 (2001)) ("Machala" or "the Machala reference") is cited in the rejection. Applicants respectfully assert that the Machala reference is not prior art to the present application, which was filed January 15, 2001.

Applicants disagree with the rejection. Nonetheless, in an effort to expedite prosecution of the application, Applicants have amended claim 1 to recite methods for making a hypermutable plant or yeast cell *in vitro* by exposing the cell to an anthracene compound. Even assuming that the requisite motivation to combine the cited references exists, which Applicants deny (*see infra*), nowhere in the cited references is there a teaching or suggestion of application of anthracene derivatives to plant or yeast cells as presently claimed.

To establish a *prima facie* case of obviousness, three requirements must be satisfied: first, there must be some suggestion or motivation to modify the reference or to combine the reference teachings; second, there must be a reasonable expectation of success for achieving the claimed invention and its particular results; and, third, the prior art references must teach or suggest all the claim limitations. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

The LaVoie reference describes the mutagenic effect of anthracene compounds on *Salmonella typhimurium* cells in the presence and absence of the S-9 fraction of rat livers. As previously noted, the Hubbard reference describes exposure of bacterial cells to dimethylanthracene in the presence of hepatocytes to approximate metabolic activation of the chemical *in vivo*. In contrast to the Hubbard and LaVoie references, each of the Krahn, Wigley, and Slaga references describes mutagenesis systems for evaluating the mutagenicity

of chemical compounds on mammalian cells. The Krahn reference describes an assay for evaluating the mutagenic effect of anthracene derivatives activated by the 9000g supernatant fraction of rat liver on Chinese hamster ovary cells. The Wigley reference describes an assay for testing mutagenicity on chemical compounds activated by lethally irradiated BHK21 cells on V79 cells. The Slaga reference describes a mutagenicity assay for evaluating the mutagenic effect of chemical compounds in the presence or absence of irradiated hamster embryo cells on V79 cells.

Applicants respectfully assert that the requisite motivation to combine the cited references has not been demonstrated. The Krahn reference states that mammalian cells and bacteria may differ in their responses to given chemical compounds. (Krahn, page 41.) Thus, the skilled artisan seeking to evaluate the mutagenicity of a chemical agent on mammalian cells would not have referred to a study that evaluates the mutagenicity of agents on bacterial cells. In other words, the skilled artisan would not have been motivated to combine any of Krahn, Wigley, or Slaga, which evaluate the mutagenicity of chemical agents on mammalian cells, with either of the Hubbard or LaVoie references, which evaluate the mutagenicity of chemical agents on bacterial cells.

In addition, no motivation to combine the Hubbard and LaVoie references has been established. The Hubbard reference explains that freshly isolated hepatocytes are utilized in the mutagenesis assay *as an alternative* to the S9 fraction employed in the methods of the LaVoie reference for metabolic activation of the hydrocarbon compounds. As the methods of Hubbard and LaVoie are alternatives to one another, the skilled artisan would not have been motivated to combine the teachings of the two references.

The Wigley reference teaches that metabolisis of hydrocarbons by BHK21 cells yields different results than those obtained in the presence of liver enzymes. (Wigley, page 691.) Wigley thus identifies BHK21 cells as an alternate activating factor to liver enzymes. As liver enzymes are utilized in the methods of both the Hubbard and LaVoie references to activate the hydrocarbons evaluated therein, one of skill in the art would not have been motivated to combine the Wigley reference with either of Hubbard or LaVoie.

Additionally, the Krahn reference asserts that the forward mutational system employed therein may be more akin to *in vivo* carcinogenic events than reverse mutational systems, such as those employed in the methods of the Hubbard and LaVoie references.

Thus, one of ordinary skill in the art would not have been motivated to combine the Krahn reference with either of Hubbard or LaVoie.

Because the cited references fail to teach or suggest the presently claimed methods and because no motivation to combine the cited references has been demonstrated, a *prima facie* case of obviousness of claims 1 and 4-13 has not been established on the record. Withdrawal of the rejection is respectfully requested.

III. Claims 23, 24, and 27-29 are patentable over either of the Hubbard or LaVoie reference in view of either the Krahn, Wigley, or Slaga reference, and further in view of the Chakravarti reference.

Claims 23, 24, and 27-29 are rejected under 35 U.S.C. § 103 for alleged obviousness over the Hubbard or LaVoie reference in view of any one of the Krahn, Wigley, and Slaga references, and further in view of Chakravarti *et al.* (*PNAS*, 92:10422-10426 (1995)) ("Chakravarti" or "the Chakravarti reference"). Applicants note that the Machala reference also is cited in the rejection but respectfully assert that Machala is not prior art to the present application, which was filed January 15, 2001. Applicants traverse the rejection.

Claims 23, 24, and 27-29 recite methods for generating a mutation in a gene of interest by exposing a cell having the gene of interest to a chemical mismatch repair inhibitor *in vitro*, the mismatch repair inhibitor being an anthracene having the recited formula, and testing the cell to determine if the gene of interest is mutated.

The primary references relied upon in the alternative are Hubbard and LaVoie. The Hubbard reference describes exposure of bactieral cells to dimethylanthracene in the presence of hepatocytes. Mutagenicity of the hepatocytes is nowhere taught or suggested. The LaVoie reference describes the mutagenic effect of anthracene compounds on *Salmonella typhimurium* cells in the presence and absence of the S9 fraction of rat livers and the tumor-initiating activity of anthracene compounds on mouse skin. Neither of the primary references teaches or suggests a step of testing the cell exposed to the mutagen*in vitro* to determine whether a gene of interest comprises a mutation.

The secondary references relied upon by the Examiner fail to remedy the deficiency of the primary references. In contrast to the Hubbard and LaVoie references, each of the Krahn, Wigley, and Slaga references describes mutagenesis systems for evaluating the

mutagenicity of chemical compounds on mammalian cells. The Krahn reference describes an assay for evaluating the mutagenic effect of anthracene derivatives activated by the 9000g supernatant fraction of rat liver on Chinese hamster ovary cells. The Wigley reference describes an assay for testing mutagenicity on chemical compounds activated by lethally irradiated BHK21 cells on V79 cells. The Slaga reference describes a mutagenicity assay for evaluating the mutagenic effect of chemical compounds in the presence or absence of irradiated hamster embryo cells on V79 cells. No teaching or suggestion of a step of testing the cell to determine whether the gene of interest harbors a mutation following exposure to the anthracene derivative is present in any of the Krahn, Wigley, or Slaga references.

The Examiner relies on the Chakravarti reference for the alleged teaching of the step of testing the cell to determine whether the gene of interest comprises a mutation. The Chakravarti reference does not, however, teach a step of identifying mutations in a gene of interest in a cell exposed to a chemical agent *in vitro*, as presently claimed. Rather, that reference identifies mutations in the *c-H-ras* gene associated *in vivo* with papillomas induced by several aromatic hydrocarbons. In other words, the Chakravarti reference teaches a step of identifying mutations in a gene of interest associated with *in vivo* tumorigenicity.

Moreover, the Chakravarti reference provides no motivation to combine with any of the Wigley, Slaga, Krahn, or Hubbard references to yield a method involving a step of identifying mutations in a gene of interest in cells in culture in the absence of demonstrated *in vivo* tumorigenicity. Mutagenic activity of a chemical agent in cell culture does not necessarily correlate to tumorigenicity *in vivo*. For example, the LaVoie reference teaches that, while 9,10-dimethylanthracene is a potent mutagen, it has weak tumor-initiating activity. (LaVoie reference, Table I and page 1487). Similarly, the Slaga reference teaches that mutagenic activity of chemical agents in bacteria does not always correlate to tumor-initiating activity. (Slaga reference, page 1703). Without the hallmark of tumorigenicity, the skilled artisan would not be motivated by the Chakravarti reference to test cells exposed *in vitro* to a chemical agent for a mutation in a gene of interest. Thus, the skilled artisan would not have been motivated to combine the methods of Krahn, Slaga, Wigley, or Hubbard, wherein no tumorigenicity is shown, with the method of Chakravarti, which requires tumorigenicity as a touchstone for identification of mutations associated therewith.

Moreover, the Krahn reference states that mammalian cells and bacteria may differ in their responses to given chemical compounds. (Krahn, page 41.) Thus, the skilled artisan seeking to evaluate the mutagenicity of a chemical agent on mammalian cells would not have referred to a study that evaluates the mutagenicity of agents on bacterial cells. In other words, the skilled artisan would not have been motivated to combine any of Krahn, Wigley, Slaga, or Chakravarti, which evaluate the mutagenicity of chemical agents on mammalian cells, with either of the Hubbard or LaVoie references, which evaluate the mutagenicity of chemical agents on bacterial cells.

As no motivation to combine the cited references has been established and, in any event, the presently claimed methods are not taught or suggested by the cited references, Applicants respectfully assert that a *prima facie* case of obviousness has not been established on this record. Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully submitted,

Date: April 22, 2004

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